at position 470 although the reduction in activity is not generally sufficient to result in CF, the diagnosis of which is based in part on clinical criteria. Data from this study indicate that mutations in the *CFTR* gene may be associated with the development of CRS in the general population. The importance of CFTR in normal sinus epithelium function is evident from the fact that CRS occurs in almost all CF patients. Less severe decreases in CFTR activity, as may occur in individuals that are heterozygous for a CF mutation (particularly if they also have a variant *CFTR* allele at the other locus), may lead to CRS in the absence of CF. While not wishing to be bound by any theory, reduced CFTR activity may lead to abnormal viscosity and electrolyte composition of sinus secretions. Such abnormalities may increase the likelihood that rhinosinusitis will develop initially and/or that it will become chronic. These findings suggest that agents such as those described herein, which increase the functional activity of mutant CFTR, may be useful for prophylaxis and/or treatment of CRS.

It is noted that diagnosis of sinusitis is based at least in part on clinical criteria, and that various classification schemes may be applied (See, e.g., International Rhinosinusitis Advisory Board. "Infectious rhinosinusitis in adults: classification, etiology and management." *Ear, Nose, Throat J.* 76(12 suppl):1-22). Determinations of whether a given patient suffers from a particular subtype may vary, and it is likely that certain individuals suffering from rhinosinusitis who carry a CF allele and/or CF variant will not be classified as having CRS but rather as having one of the other subtypes. Thus the agents described herein may also be useful for treatment or prophylaxis in individuals who suffer from rhinosinusitis that has not been classified as chronic rhinosinusitis. Such agents would be particularly appropriate for patients with rhinosinusitis who are CF carriers, patients who are CF carriers and have a *CFTR* variant at the second locus, and patients who are homozygous for a *CFTR* variant. As is well known in the art, patients who are CF carriers and/or have a *CFTR* variant may be identified by DNA analysis as described, for example, in Wang, X., *et al.* Thus the present invention provides a method for treating rhinosinusitis comprising administering an agent that permits the release of proteins from the endoplasmic reticulum. In certain embodiments of the invention the method further comprises providing an individual suffering from rhinosinusitis, e.g., from chronic rhinosinusitis. In certain embodiments of the invention such individual carries a CF mutation, e.g., ΔF508. In certain embodiments of the invention the individual carries a CF variant, e.g., M470V.

In certain embodiments of the invention the method comprises administering an

agent that permits the release of proteins from the endoplasmic reticulum, an agent that decreases or inhibits the activity of UDP glucose:glycoprotein glycosyl transferase, an agent that decreases or inhibits activity of the endoplasmic reticulum Ca^{++} ATPase, an agent that lowers the concentration of Ca^{++} in the endoplasmic reticulum, an agent that causes release of Ca^{++} from the ER, an agent that stimulates or increases IP_3 receptor activity, an agent that decreases or inhibits calnexin functional activity, or an agent that increases or activates ryanodine receptor activity. Particular agents that may be used in the practice of the invention include thapsigargin or a derivative thereof, cyclopiazonic acid or a derivative thereof, DBHQ or a derivative thereof, and halothane or a derivative thereof.

In certain embodiments of the invention the agent is delivered intranasally according to methods well known in the art and widely used for treatment of allergies, etc. Of course the agent can be delivered by various other means as well.

Applications for release of normally assembled or folded proteins from the ER

As described above, the present invention contemplates enhancing release of misassembled and/or misfolded proteins from the ER. According to certain embodiments of the invention release is enhanced by lowering the Ca^{2+} concentration within the ER lumen. While not wishing to be bound by any theory, it is possible that lowering the ER Ca^{2+} concentration may alter or interfere with the activity of chaperone proteins that would otherwise bind to a misassembled or misfolded protein and prevent its release from the ER.

The interaction of normal and mutant proteins with various ER chaperones is a subject of ongoing investigation. For example, in the case of CFTR it appears that the protein interacts with at least two ER chaperones, heat shock protein 90 (hsp90) and heat shock cognate 70 (hsc70) (refs). In a manner that is not yet fully understood and which depends at least in part on the primary sequence of the newly synthesized CFTR protein (e.g., whether it is wild type or mutant), these interactions ultimately lead to release of the protein from the ER, retention of the protein in the ER, and/or ubiquitination of the protein and ultimately ubiquitin-dependent degradation by the proteasome (refs). Only approximately 25% of the wild type CFTR protein attains a stable conformation (stable B) that allows it to exit the ER, while the remainder is ubiquitinated in the ER and thereby targeted for degradation (ref). In the case of folding mutants an even smaller fraction of the protein reaches the stable B form. Very little if any ΔF508 CFTR protein reaches stable B, and thus essentially all the protein is

ubiquitinated and degraded. While not wishing to be bound by any theory, it is possible that association with chaperones is involved both in proper folding of CFTR protein and in allowing ubiquitination of both normal and mutant CFTR. Thus it is possible that an agent that alters or interferes with chaperone activity may lead to decreased ubiquitination of wild type CFTR and thereby allow a greater amount of wild type CFTR to exit the ER. In the case of an individual who carries one wild type allele of the CFTR gene and one allele that encodes a misfolded CFTR protein, it is possible that treatment with such an agent would lead to increased cell surface expression of wild type CFTR, thus compensating for any decrease in cell surface expression resulting from the mutation.

It is therefore contemplated that the compositions and methods of the present invention may be useful not only to increase release of misassembled and/or misfolded proteins from the ER but also to increase release of wild type proteins from the ER, particularly in cases where a large fraction of the wild type protein is not released (as is the case for the normal CFTR protein). The compositions and methods may similarly be useful to increase release of mutant proteins from the ER even in cases in which the mutant proteins are not necessarily misassembled and/or misfolded.

Thus the compositions and methods of the invention may be used to treat individuals suffering from a condition associated with misassembly or misfolding of a protein, in whom one copy of a particular gene associated with the condition encodes a misassembled or misfolded protein while the other copy encodes a wild type protein or a mutant protein where the mutation does not result in misassembly or misfolding but instead results in a protein that functions at less than wild type levels for some other reason. As described above, such individuals may include individuals with rhinosinusitis, where the individuals have a mutation in at least one copy of the CFTR gene, regardless of whether the mutation results in synthesis of a misfolded protein. Such individuals also include individuals suffering from CF, where the individuals have different mutations in their two copies of the CFTR gene, only one of which results in production of a misfolded protein.

J. <u>Applications For Non-CF Protein Release</u>

In addition to CF, a large and growing list of disease states is associated with protein retention in the ER (Amara J, Cheng S and Smith A., <u>Trends in Cell Biol</u> 2:145-149 (1992); Bychkova V and Ptitsyn O, Folding intermediates are involved in